REMARKS

This document is filed in reply to the final office action dated August 30, 2004 ("Office Action") and the Advisory Action dated January 27, 2005 ("Advisory Action").

In the response to the Office Action mailed on December 30, 2004, Applicants proposed amending the Specification and a number of claims. In the following Advisory Action, the Examiner declined to enter the amendments Applicants hereby file a Request for Continued Examination under 37 CFR § 1.114(d).

Applicants have inserted into the specification two sequence identifiers "SEQ ID NO: 12" and "SEQ ID NO: 13." The sequence of SEQ ID NO: 12, i.e., nucleotides 81889 - 83238 of E. coli genome (GenBank Accession No. AP002562), was presented in the substitute sequence listing filed with the response dated June 29, 2004. SEQ ID NO: 13 corresponds to nucleotides 768-974 of SEQ ID NO: 12 and represents the open reading frame ECs3459.[1] It was included in a second substitute sequence listing, which was filed with the response to the Office Action date December 30, 2004.

Applicants have amended claims 1, 8, and 36, which recite PCR products, to specify that the PCR products specifically hybridize to SEQ ID NO: 5, 6, 7, or 8, or the complete complement thereof. Support for this amendment can be found at page 2, lines 1-5; page 3, line 26 through page 4, line 14; and page 11, line 20 through page 13, line 3 of the Specification. Finally, Applicants have also amended claims 1, 8, 15, and 36-39 to promote clarity. No new matter has been added.

Claims 1-15 and 23-43 are pending. Claims 27-35 have been withdrawn from further consideration for covering a non-elected invention. Claims 1-15, 23-26, and 36-43 are now under examination. Reconsideration of this application is requested in view of the following remarks. Among the four sections below, the first two sections "Rejection under 35 U.S.C. § 112, second paragraph" and "Rejection under 35 U.S.C. § 102(b)" are reproduced from the counterpart sections in the response mailed on December 30, 2004.

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[1] The open reading frame ECs3459 corresponds to nucleotides 82656-82963 of GenBank Accession No. AP002562 (SEQ ID NO: 12). See Exhibit A attached hereto. In other words, it corresponds to nucleotides 768-974 of SEQ ID NO: 12.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 1-15, 23-26, and 36-43 for indefiniteness. See the Office Action, page 7, last paragraph. In view of the above amendments, Applicants submit that the rejection has been overcome.

Rejection under 35 U.S.C. § 102(b)

The Examiner rejected claim 15, which recites "SEQ ID NOs.: [5 and 6] and sequences complementary thereto" for being anticipated by GenBank Accession Nos. AF175847 and AX002476. See the Office Action, page 9, lines 6 and 7, and lines 15 and 16. It is the Examiner's position that the recitation "sequences complementary thereto" does not "limit the claim to sequences that contains the complete complement of SEQ ID NO: [5 or 6]."

Applicants have amended claim 15 to recite "complete complement," and submit that, claim 15, as amended, is not anticipated by the two GenBank Accession Nos.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 8-14 and 36-38 for failing to comply with the written description requirement. Applicants have amended claims 8 and 36, and will discuss claim 8 first.

Claim 8, as amended, covers a nucleic acid prepared by PCR amplification from an E. coli nucleic acid template with a pair of primers containing SEQ ID NOs: 1 or 3 and SEQ ID NO: 2 or 4. The nucleic acid must hybridize under highly stringent conditions to SEQ ID NO: 5, 6, 7, or 8, or the complement thereof.

Applicants would like to point out that the Specification provides sufficient written description for amended claim 8, as evidenced by the U.S. Patent and Trademark Office's own guidelines on the subject: Synopsis of Application of Written Description Guidelines ("Guidelines"), www.uspto.gov/web/menu/written.pdf. Example 10 of the Guidelines illustrates a hypothetical situation that tracks the present case precisely. More specifically, it includes the following three claims:

> Claim 1: A process for producing an isolated polynucleotide comprising hybridizing SEQ ID NO: 10 to genomic DNA in 6XSSC and 65°C and isolating the DNA polynucleotide detected with SEQ ID NO: 10.
>
> Claim 2: An isolated DNA polynucleotide that hybridizes with SEQ ID NO: 10.
>
> Amended Claim 2: The isolated DNA polynucleotide prepared according to the process of claim 1.

Note that amended claim 2, a product-by-process claim, is drawn to genomic DNA that must hybridize under a highly stringent condition to SEQ ID NO: 10. Like this claim, claim 8, also a product-by-process claim, is drawn to genomic DNA that must hybridize under a highly stringent condition to SEQ ID NO: 5, 6, 7, or 8, or the competent thereof.[2] Just as in Example 10,

> [t]he specification also teaches that SEQ ID NO: [5, 6, 7, or 8, or the competent thereof] is a [genomic] marker [of E. coli] and that any DNA which hybridizes under specified stringent conditions to SEQ ID NO: [5, 6, 7, or 8, or the competent thereof] will be useful as a marker for detecting the presence of [E. coli]. The specification also teaches how to produce DNAs including genomic DNAs which hybridize to SEQ ID NO: [5, 6, 7, or 8, or the competent thereof] and isolation of said DNAs. The specification presents an example where a genomic DNA is probed with SEQ ID NO: [5, 6, 7, or 8, or the competent thereof] under the specified stringent conditions ... and the genomic DNA which hybridizes under these conditions is isolated and is sequenced.
> ...
>
> A review of the full content of the specification indicates that the essential feature of the claimed invention is a process of obtaining a nucleic acid sequence which is identified [by PCR] ... and a polynucleotide that hybridizes with SEQ ID NO: [5, 6, 7, or 8, or the competent thereof]. The specification and the general state of the art indicate that the general process of producing nucleic acids through [PCR with specific primers and] hybridization with probes was routine at the time of filing.
> ...

[2] The processes recited in amended claim 2 of Example 10 of the Guidelines and in claim 8 of the instant application are hybridization and PCR, respectively. Although the two processes are different, the two nucleic acid claims include the same structural limitation, i.e., a highly stringent hybridization condition. Thus, the guidance in Example 10 is applicable to the issue at hand.

Just as in Example 10,

> The specification presents an example where [as many as 64] species ha[ve] been reduced to practice, ... based on [PCR and] hybridization with SEQ ID NO: [5, 6, 7, or 8]. Therefore the disclosed species within the genus ha[ve] been adequately described. Now turning to the genus analysis, the art indicates that there is no substantial variation within the genus because of the stringency of hybridization conditions which yields structurally similar molecules. The [64] disclosed species [are] representative of the genus because reduction to practice of th[ese] species, considered along with the defined hybridization conditions and the level of skill and knowledge in the art, are sufficient to allow the skilled artisan to recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus.
>
> ...
>
> **Conclusion:**
> Claim 1 is adequately described.
>
> Claim 2 should be rejected as lacking adequate written description following the analysis described above.
>
> **Note: Applicant may overcome the written description rejection of the product by, for example, substituting claim 2 with a product by process claim such as the [amended claim 2 presented above].**

In view of the very clear instructions set forth in the Synopsis, Applicants submit that claim 8 meets the written description requirement. Claims 9-14, dependent from claim 8, specify the sequences or lengths of the primers recited in claim 8. By the same token, they also meet the written description requirement.

The Examiner also rejected claims 36-39, drawn to a set of nucleic acids that include a third nucleic acid, on the same grounds discussed above. Applicants have amended claim 36 to specify that the third nucleic acid must specifically hybridize under highly stringent conditions to SEQ ID NO: 5, 6, 7, or 8, or its complete complement. For the same reasons provided above, claim 36 also meets the written description requirement. So do claims 37-39, which depend from claim 36 and further specify the length of the third nucleic acid.

Rejection under 35 U.S.C. § 103(a)

The Examiner rejected claims 1-3, 5, 6, 8-15, and 36-39 for obviousness over GenBank Accession No. AE005490, GenBank Accession No. AE000346, GenBank Accession No. Z70523, and GenBank Accession No. D90887, in view of Buck et al. Biotechniques, 1999, 27(3): 528-536 ("Buck"), U.S. Patent 5,374,718 to Hammond et al. ("Hammond"), U.S. Patent 5,693,769 to Hogan ("Hogan"), and Tijhie et al., J. Micobiol. Meth. Vol. 18, pp 137-150, 1993 ("Tijhie"). See the Office Action, the paragraph bridging pages 10 and 11.

Applicants respectfully traverse and will first discuss claim 1, an independent claim, and claim 36 dependent therefrom. Independent claim 1 is drawn to a set of nucleic acids including a first nucleic acid and a second nucleic acid that contain SEQ ID NO: 1 or 3 and SEQ ID NO: 2 or 4, respectively. The first and second nucleic acids as primers participate in a polymerase chain reaction (PCR), with an Escherichia coli nucleic acid as a template, to generate a PCR product. Claim 36 recites a third sequence that contains one of SEQ ID NOs: 5-8.

According to the Examiner, it would have been obvious to one skilled in the art to combine all of the cited references and to select SEQ ID NOs: 1-8 from the above-mentioned 4 GenBank Accession Nos. for generating the claimed nucleic acid set. In the response to the Office Action, Applicants rebutted the rejection by presenting an unexpected property exhibited by the claimed nucleic acids. Nonetheless, the Examiner maintained the rejection. According to her,

> the instant rejection has not been applied to claims 4, 7, and [23]-26[, which are drawn to primers or probes having one of SEQ ID NOs: 1-8 only]. As exemplified by the specification, [sequences covered by these claims] exhibited unexpected results in that they were capable of detecting E. coli and not a large number of other genus and species of bacteria .... As such, [the] claims directed to the scope of the unexpected results ... are allowable over the cited prior art. However, the remaining claims are broader in scope [as they cover primers or probes having additional sequences other than SEQ ID NOs: 1-8] ... additional sequences on either side of SEQ ID NOS: 1-8 would be expected to change the hybridization specificity of the resulting sequences as compared to those exemplified by the specification. See the Office Action, the paragraph bridging pages 13 and 14.

Put differently, it is the Examiner's position that rejected claim 1 may cover PCR primers that do not hybridize to the complements of SEQ ID NOs: 1-4, and, therefore, would not generate E. coli-specific products, i.e., fail to exhibit the just-mentioned unexpected results.

Applicants disagree. Indeed, it is clear from the Specification that the PCR primers at issue exclude those that do not hybridize to the complements of SEQ ID NOs: 1-4. More specifically, the Specification explicitly describes two scenarios: (1) only corresponding E. coli sequences can be added to either side of core SEQ ID NO: 1-4, and (2) none-E. coli (i.e., heterologous) sequences can be added to the 5' end of each core sequence. See, page 3, lines 20-25. In scenario (1), the PCR primers must hybridize to E. coli sequences having the complements of SEQ ID NO: 1-4, regardless of any "additional sequences." Referring to scenario (2), Applicants would like to point that a 5' end heterologous sequence, as well known in the art, does not interfere with a PCR primer's hybridization specificity or chain-extending activity. Given this teaching and state of the art, one skilled in the art would recognize that the PCR primers in claim 1 must hybridize to E. coli sequences having the complements of the core sequences in presence of the "additional sequences." Further, claim 1 limits the lengths of the PCR primers to between 18 and 40 nucleotides. As a result, each core sequence, whose length ranges between 18 and 24 nucleotides, accounts for a dominant fraction of each primer. It follows that each primer retains the core sequence's hybridization specificity and also exhibits the above-mentioned unexpected results, i.e., capable of detecting E. coli and not a large number of other bacteria. Thus, claim 1 is also "allowable over the cited prior art." In the sole interest of moving this case toward allowance, Applicants have narrowed the PCR primers in claim 1 to those that must generate E. coli-specific sequences.

For the remarks and amendments above, it is submitted claim 1, as well as claim 36, is non-obvious over the cited references. Independent claim 8 is drawn to PCR products generated by the primers in claim 1. Applicants have amended this claim in the same manner described above. For the same reasons set forth above, it is non-obvious. So are claims 2, 3, 5, 6, 9-14, or 37-39, all of which depend from claim 1 or 8. Claim 15 is drawn to a set of nucleic acids

consisting of SEQ ID NOs: 5-8. As the Examiner already indicated that SEQ ID NOs:5-8 are non-obvious, claim 15 is also non-obvious.

CONCLUSION

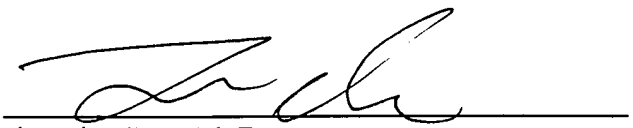
In view of the above amendments and remarks, as well as the remarks provided in the last response, Applicants submit that the grounds for the rejections asserted by the Examiner have been overcome, and that claims, as pending, define subject matter that is sufficiently described, definite, novel, and non-obvious. On this basis, it is submitted that allowance of this application is proper, and early favorable action is solicited.

This response is being filed concurrently with a Request for Continued Examination and the required $395.00 fee, a Petition for Three-Month Extension of Time with the required fee of $900 (a Petition for One-Month Extension of Time with the required fee of $120 was previously filed on December 30, 2005).

Please apply any other charges to Deposit Account No. 06-1050, referencing Attorney Docket No. 12875-005001.

Respectfully submitted,

Date: 2-28-2006



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1: AP002562. Reports Escherichia coli ... [gi:13362858]

LOCUS AP002562 207 bp DNA linear BCT 20-MAR-2004
DEFINITION Escherichia coli O157:H7 DNA, complete genome, section 13/20.
ACCESSION AP002562 REGION: 82656..82862
VERSION AP002562.1 GI:13362858
KEYWORDS .
SOURCE Escherichia coli O157:H7
ORGANISM Escherichia coli O157:H7
Bacteria; Proteobacteria; Gammaproteobacteria; Enterobacteriales; Enterobacteriaceae; Escherichia.
REFERENCE 1
AUTHORS Makino,K., Yokoyama,K., Kubota,Y., Yutsudo,C.H., Kimura,S., Kurokawa,K., Ishii,K., Hattori,M., Tatsuno,I., Abe,H., Iida,T., Yamamoto,K., Ohnishi,M., Hayashi,T., Yasunaga,T., Honda,T., Sasakawa,C. and Shinagawa,H.
TITLE Complete nucleotide sequence of the prophage VT2-Sakai carrying the verotoxin 2 genes of the enterohemorrhagic Escherichia coli O157:H7 derived from the Sakai outbreak
JOURNAL Genes Genet. Syst. 74 (5), 227-239 (1999)
MEDLINE 20198780
PUBMED 10734605
REFERENCE 2
AUTHORS Ohnishi,M., Murata,T., Nakayama,K., Kuhara,S., Hattori,M., Kurokawa,K., Yasunaga,T., Yokoyama,K., Makino,K., Shinagawa,H. and Hayashi,T.
TITLE Comparative analysis of the whole set of rRNA operons between an enterohemorrhagic Escherichia coli O157:H7 Sakai strain and an Escherichia coli K-12 strain MG1655
JOURNAL Syst. Appl. Microbiol. 23 (3), 315-324 (2000)
MEDLINE 20557356
PUBMED 11108008
REFERENCE 3
AUTHORS Yokoyama,K., Makino,K., Kubota,Y., Watanabe,M., Kimura,S., Yutsudo,C.H., Kurokawa,K., Ishii,K., Hattori,M., Abe,H., Iida,T., Yamamoto,K., Hayashi,T., Yasunaga,T., Honda,T., Sasakawa,C. and Shinagawa,H.
TITLE Complete nucleotide sequence of the prophage VT1-Sakai carrying the Shiga toxin 1 genes of the enterohemorrhagic Escherichia coli O157:H7 strain derived from the Sakai outbreak
JOURNAL Gene 258 (1-2), 127-139 (2000)
MEDLINE 20564182
PUBMED 11111050
REFERENCE 4
AUTHORS Hayashi,T., Makino,K., Ohnishi,M., Kurokawa,K., Ishii,K., Yokoyama,K., Han,C.-G., Ohtsubo,E., Nakayama,K., Murata,T., Tanaka,M., Tobe,T., Iida,T., Takami,H., Honda,T., Sasakawa,C., Ogasawara,N., Yasunaga,T., Kuhara,S., Shiba,T., Hattori,M. and Shinagawa,H.
TITLE Complete genome sequence of enterohemorrhagic Escherichia coli O157:H7 and genomic comparison with a laboratory strain K-12
JOURNAL DNA Res. 8 (1), 11-22 (2001)
MEDLINE 21156231
PUBMED 11258796
REFERENCE 5 (bases 1 to 207)

AUTHORS Hattori,M., Ishii,K. and Shiba,T.
TITLE Direct Submission
JOURNAL Submitted (26-JUN-2000) Masahira Hattori, Kitasato Institute for Life Sciences, Kitasato University; Kitasato 1-15-1, Sagamihara, Kanagawa 228-8555, Japan
(E-mail:hattori@genome.ls.kitasato-u.ac.jp, URL:http://genome.ls.kitasato-u.ac.jp/, Tel:81-42-778-8194, Fax:81-42-778-8193)
COMMENT genome project
This work was done in collaboration with Tetsuya Hayashi, Makoto Ohnishi, Keisuke Nakayama (Miyazaki Medical College), Kozo Makino, Ken Kurokawa, Katsushi Yokoyama, Masashi Tanaka, Takeshi Honda, Teruo Yasunaga, Hideo Shinagawa (Osaka University), Takahiro Murata (Shinshu University), Chang-Gyun Han, Eiichi Ohtsubo, Toru Tobe, Chihiro Sasakawa (University of Tokyo), Hideto Takami (Japan Marine Science and Technology Center), Naotake Ogasawara (Nara Institute of Science and Technology), Satoru Kuhara (Kuyshu University), and supported by the Research for the Future Program of the Japan Society for the Promotion of Science.
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